REMARKS

Claim 82 is pending in the application. In the present amendment, the specification is amended at pages 50 and 81 to correct typographical errors. No new matter has been added by these corrective amendments. Entry of the present amendment is respectfully requested.

Rejection of Claim 82 under 35 U.S.C. § 103(a)

In the Final Office Action mailed on April 8, 2005, claim 82 was rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 3,389,051 to Kagan ("Kagan") in view of CA117:239545.

Applicants' claim 82 recites the following:

> A pharmaceutical composition for reducing skin pigmentation, comprising a skin pigmentation reducing effective amount of a compound that effects an alteration in late endosomal/lysosomal trafficking in a skin cell and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is formulated for topical administration, and wherein the compound that effects the alteration in late endosomal/lysosomal trafficking is selected from the group consisting of [chemical structures II-VIII].

Kagan discloses methods for reducing cholesterol in the body by administering particular chemical compounds (col. 1, lines 1-20). The disclosure of Kagan is focused on compositions for oral administration or injection for reducing cholesterol levels, and does not teach or suggest *topical* administration of the disclosed cholesterol lowering compositions for *any* purpose (*see, e.g.,* col. 4, lines 69-75; col. 5, lines 61-66; Examples 1-8; claims 1-2).

CA117:239545 discloses a transdermal and topical delivery system based on biocompatible polyurethane elastomers. CA117:239545 does not disclose administration of any of the compounds recited in claim 82.

To support a *prima facie* case of obviousness, the cited references must teach or suggest every element of the claimed invention, and there must be some suggestion or motivation to combine the teachings of the cited references. The motivation to combine must be found in the

prior art, and must not be based on impermissible hindsight in view of Applicants' disclosure. MPEP § 2142.

Claim 82 is not *prima facie* obviousness over Kagan and CA117:239545, alone or in combination. Neither of the cited references provides any teaching regarding a topical pharmaceutical composition for reducing skin pigmentation with a compound that effects an alteration in late endosomal/lysosomal trafficking in a skin cell as claimed. The Office Action of September 11, 2003 states that Kagan discloses a compound corresponding to compound VIII of Applicants' claim 82, and that it would have been obvious to deliver this compound in a topical delivery system as disclosed by CA117:239545. The Final Office Action of April 8, 2005 states further that Kagan's failure to disclose a topical or transdermal delivery system does not mean the reference intended to exclude such delivery systems, because the reference does not state that the disclosed compounds cannot be used in such forms.

Applicants respectfully submit that the Examiner still has not satisfied the burden of identifying an affirmative motivation to combine the teachings of Kagan, relating to oral or parenteral cholesterol lowering compositions, with the teachings of CA117:239545 directed to a transdermal and topical delivery system, *other than hindsight based on Applicants' disclosure.* Kagan's failure to explicitly prohibit topical application of the disclosed compounds does not provide the requisite motivation to combine. Indeed, Kagan effectively teaches away from the use of transdermal or topical delivery systems such as the one disclosed by CA117:239545.

Kagan discloses a wide range of oral and parenteral formulations for administering the disclosed cholesterol lowering compounds (*see, e.g.,* col. 4, line 69 - col. 5, line 66; Examples 1-8). For example, at column 4, lines 70-75, Kagan states that "the novel compositions are suitably presented for administration in unit dosage form as tablets, pills, capsules, powders, wafers, cachets, granules, sterile parenteral solutions or suspensions in aqueous or oil vehicles, oral aqueous or oil dispersions, including syrups and elixirs, and the like." However, Kagan does not disclose compositions for topical administration, although the general concept of topical pharmaceutical compositions has been well known for many years. By disclosing numerous oral and parenteral dosage forms but failing to disclose topical formulations, the teachings of Kagan suggest to one of ordinary skill in the art that the disclosed compositions would not be effective for their intended purpose when administered topically. Accordingly, the only possible motivation to combine the compounds disclosed by Kagan with the topical and transdermal

delivery system disclosed in CA117:239545 would be based on *improper hindsight in view of Applicants' disclosure.*

Furthermore, even if a *prima facie* case of obviousness had been established, it would be rebutted by the unexpected effects of the claimed compositions in reducing skin pigmentation, as described in the specification (*see, e.g.*, page 7, lines 8-15; page 8, line 32 – page 11, line 3; page 16, lines 21-31; page 18, lines 13-16; page 19, lines 1-6; page 50, lines 23-29; page 56, lines 6-12; Example 6; and Figures 15-16). The inventors determined that agents capable of modifying late endosomal/lysosomal trafficking (such as the compounds recited in claim 82) are useful for reducing skin pigmentation, because they alter the trafficking of proteins necessary for melanin synthesis, and decrease melanin production. Prior to this discovery, one of ordinary skill in the art would not have expected the compounds recited in claim 82 to have an effect on melanin production, and thus would not have been motivated to apply the compounds in topical formulations for reducing skin pigmentation. The experimental results described in Example 6 and illustrated in Figures 15-16 demonstrate the previously unknown and unexpected effect on skin pigmentation of the compounds recited in claim 82. These results demonstrate that compounds II-VIII significantly decrease melanin production in melanocytes (*see* Specification, page 79, lines 18-27; page 50, lines 23-29; and Figures 15-16). Thus, as described and demonstrated by experimental evidence presented in the specification, the claimed topical compositions provide the previously unknown and beneficial effect of decreasing melanin production, and thus reducing skin pigmentation.

In sum, *prima facie* obviousness has not been established, and even if there were a *prima facie* case, it would be rebutted by the unexpected effects of the claimed compositions in reducing skin pigmentation. Accordingly, claim 82 is not obvious in view of the cited references alone or in combination, and Applicants respectfully request that the present rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Conclusion

In view of the arguments set forth above, Applicants respectfully submit that the rejections contained in the Final Office Action mailed on April 8, 2005 have been overcome, and that the pending claim is in condition for allowance.

Please charge the $790.00 fee for this Request for Continued Examination to our Deposit Account No. 08-0219. No other fees are believed to be due in connection with this correspondence. However, please charge any payments due or credit any overpayments to our Deposit Account No. 08-0219.

The Examiner is encouraged to telephone the undersigned at the number listed below in order to expedite the prosecution of this application.

Respectfully submitted,

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Dated: 6/29/05

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